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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/826,609	04/05/2001	Bruce L. Roberts	GA0150C	4367

24536 7590 04/25/2005

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/826,609	ROBERTS ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) 8-24 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7,25 and 26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 01/18/2005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4, 5, 7 and 25 have been amended. Claims 1-26 are pending. Claims 8-24, drawn to non-elected inventions, remain withdrawn from consideration. Claims 1-7, 25 and 26 are under consideration.

2. Text of sections of Title 35, U.S. Code not found in this action can be found in a previous action.

3. Claims 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear if the protein identified as immunogenic in section c) is the same protein being referred to in the recitation of "an immunogenic protein" in section d).

4. The rejection of claims 1 and 2 is maintained for the reasons of record stated on page 5 section 9 of the previous Office action. Applicant argues that the instant specification provides significant guidance with respect tot gene therapy vectors useful in the instant methods because the specification describes the most common vectors used at the tie of filing, such as the adenoviral vectors, the adeno-assoicated viral vectors, retroviral and non-retroviral vectors. This has been considered but not found persuasive. The previous rejection stated that the volume of distribution of the vector, rate of clearance in tissue and the in vivo consequences of altered gene expression, the fraction of the vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the stability of the mRNA produced in vivo, the amount and stability of the mRNA produced in vivo, the amount and stability of the protein produced in and the protein comparmentalization or secretory fate all contribute to the unreliability of the gene dosage, and unreliability of the dosage of the protein encoded therefrom. Applicant argues that at the time of filing Orkin reports the treatment of 597 individual by gene transfer experiments. This has been considered but not found persuasive. Applicant is taking examples out of context. What is actually on page 1, point 2 of Orkin is

2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

Thus, Orkin corroborates the examiner's contention of unreliability of the art.

Applicant argues that the Eck reference, although pointing out limitations in clinical application of gene therapy was quite positive about the utility of gene therapy. This again is not persuasive. Optimism about the eventual utility of gene therapy in no way provides an enabling disclosure for the state of the art at the time of filing of this application. In order to meet the requirements of 35 U.S.C. 112, first paragraph, it would be necessary to provide an enabling disclosure of how to use the instant claimed method clinically, because the claim require the administration to a subject in a gene delivery vehicle which clearly reads on the treatment of human patients in a clinical setting. Applicant argues that the Verma reference supports the instant ennoblement of gene therapy because said reference discloses more than 200 gene therapy trial in the U.S. This is not persuasive. What Verma actually states in reference to the 200 clinical trails is

"Although more than 200 clinical trails are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story".

Thus, Verma et al corroborate the examiner's contention of unreliability of the art.

5. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 7 has been amended to include the qualifier "with novel immunogenicity" in reference to the identified amino acid sequence. This limitation is not supported by the specification or claims as filed. The specification states (page 2. lines 5-12) that if the over expressed transcript corresponds to a protein sequence which is immunogenic then it is useful as a cancer vaccine or in adoptive immunotherapy". As such, the instant method claims would encompass amino acid sequences with both novel and non-novel immunogenicity in the inclusion of a sequence with known immunogenicity. the specification does not describe the elimination of such sequence from the group of sequences identified by virtue of being over

expressed.. One of skill in the art would reasonably conclude that applicant was not in possession of the method as amended, at the time of filing.

6. Claims 1, 3-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Frudakis et al (U.S. 6,586,570).

Claim 1 is drawn to a method comprising identifying a polynucleotide which is uniquely expressed or over expressed in a target human cancer cell as compared with a control-human non-cancer cell; determining the protein corresponding to said identifying polynucleotide; determining if said protein, or fragment thereof, is immunogenic, wherein the ability of said protein or fragment thereof to elicit an immune response against said target cancer cell is indicative of a putative cancer therapeutic effect by said protein or fragment thereof. Claim 3 embodies the method of claim 1 further comprising step d) wherein said immunogenic protein or fragment thereof is administered to a subject in an antigen-presenting cell.

Claim 4 is drawn to a method comprising the steps in order of a) identifying a polynucleotide which is uniquely expressed or over expressed in a target human cancer cell as compared with a control-human non-cancer cell; b) determining the protein corresponding to said identifying polynucleotide; c) determining if said protein, or fragment thereof, is immunogenic, wherein the ability of said protein or fragment thereof to elicit an immune response against said target cancer cell is indicative of immunogenicity; d) generating immune effector cells reactive with an immunogenic protein, and e) administering said immune effector cells to a subject, wherein the ability of said immune effector cells to elicit an immune response against said target cancer cells is indicative of a putative cancer therapeutic effect by said immune effector cells.

Claim 5 is drawn to a method comprising the steps in order of a) identifying a polynucleotide which is uniquely expressed or over expressed in a target human cancer cell as compared with a control-human non-cancer cell; b) determining the protein corresponding to said identifying polynucleotide; c) determining if said protein, or fragment thereof, is immunogenic, wherein the ability of said protein or fragment thereof to elicit an immune response against said target cancer cell is indicative of immunogenicity; d) generating antibodies reactive with an immunogenic protein; and e) administering said antibodies to a subject, wherein

the ability of said antibodies to elicit an immune response against said target cancer cells is indicative of a putative cancer therapeutic effect by said antibodies. Claim 6 embodies the method of claim 5 wherein said antibodies are monoclonal antibodies.

Claim 7 is drawn to a method to design a cancer vaccine from a sample obtained from a subject suffering from cancer, comprising identifying an amino acid sequence with novel immunogenicity which is firstly identified as uniquely expressed or over-expressed in a target human cancer cell from said subject and secondly determined as capable of eliciting and immune response against said target cell and designing a cancer vaccine corresponding to said amino acid sequence.

Frudakis et al disclose a method comprising identifying polypeptides expressed from mRNA, wherein the level of mRNA encoding the polypeptide is at least 2-fold higher in breast tumor tissue than in normal breast tissue (column 5, lines 42-46 and column 24, Table I), followed by the identification of peptides comprising B-cell and T-cell epitopes therefrom by means of known predictive methods (column 22, lines 30-45). Frudakis et al disclose that the presence of antibodies within the serum of a breast cancer patient which bind to said epitope confirms the immunogenicity of a peptide comprising the B-cell epitope in question (column 22, lines 55-57). Frudakis et al disclose that successful in vitro generation of T-cells capable of killing autologous tumor cells confirms the immunogenicity of the peptide comprising the T-cell epitope in question (column 23, lines 11-15). Frudakis et al disclose that the antigen-specific T-cells may be generated in vivo within the patient using the immunogenic portions of the disclosed polypeptides , and the resulting CD+8 CTL clones may be isolated from the patient, expanded and returned to the patient (column 18, lines 16-24). Frudakis et al disclose that peptides corresponding to the immunogenic portions of the polypeptide may be employed to generate tumor reactive T-cell subsets by selective in vitro stimulation and expansion of autologous T-cells which may subsequently transferred to the patient (column 18, lines 25-31). Frudakis et al disclose that syngenic or autologous dendritic cells may be pulsed with peptide corresponding to at least an immunogenic portion of the disclosed polypeptides and the resulting dendritic cells displaying said immunogens may either be transferred to a patient or employed to stimulate T-cells to provide antigen-specific T-cells which may in turn be administered to a patient (column 18, lines 32-43). Frudakis et al disclose that monoclonal antibodies specific for

the antigenic polypeptides of interest may be prepared (column 10, lines 52-55) and that the antibodies may be incorporated into vaccines for the treatment of breast cancer (column 15, lines 58-63). It is noted that the method disclosed by Frudakis et al included inherently include identifying proteins and peptides with novel immunogenicity, therefore the limitations of claim 7 have been met.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frudakis et al (U.S. 6,586,570) in view of Philip et al (WO 97/03703).

Claim 25 is drawn to a method comprising identifying a polynucleotide which is expressed at a higher level in a target human cancer cell as compared with a control non-cancer cell; determining the protein corresponding to said identified polynucleotide; determining if said protein is immunogenic comprising the steps of i) introducing a gene transfer vector encoding a sequence corresponding to said protein into a an antigen presenting cell (APC) under conditions whereby said encoded sequence is expressed by said antigen presenting cell; ii) culturing naive immune effector cells with said antigen presenting cell under conditions whereby said naive immune effector cells are educated to recognize antigens present on the surface of said antigen presenting cell in the context of an MHC molecule; and iii) determining if said educated immune effector cells can lyse said target cancer cell is indicative of a putative cancer therapeutic effect by said immune effector cells. Claim 26 embodies the method of claim 25 wherein said antigen presenting cell is a dendritic cell.

Frudakis et al teach all of the embodiments of claim 25 with the exception of step i) introducing a gene transfer vector encoding a sequence corresponding to said protein into a an

antigen presenting cell (APC) under conditions whereby said encoded sequence is expressed by said antigen presenting cell.

Philip et al teach that antigen presenting dendritic cells can be prepared either by pulsing or by lipofection with the relevant gene in order to elicit and immune response in a subject (page 63, lines 21-36, page 64, lines 16-28). Philip et al teach that this strategy can be used to make CTL to a tumor antigen (page 65, lines 20-26). Philip et al teach that the method successfully transferred full length genes to the dendritic cells, as evidenced by the fact that the full length mRNA was detected (page 69, lines 9-21).

It would have been prima facie obvious at the time the claimed invention was made to transfect dendritic cells with the polynucleotides identified to be uniquely expressed or over expressed in tumors in order to carry out the assay described by Frudakis et al on the determination of immunogenicity. One of skill in the art would have been motivated to do so by the teachings of Philip et al on the transfection of full length cDNA encoding the tumor antigens of interest. One of skill in the art would understand that the polypeptides identified as uniquely expressed or over expressed can be directly used in the transfection of the dendritic cells for the determination of the ability to elicit CTL, in contrast to the separate steps of determination of a T-cell epitope by predictive methods and the synthesis of the peptides predicted to be immunogenic, followed by the stripping of dendritic cells of endogenous peptides and the loading of the peptides predicted to be immunogenic. One of skill in the art would understand that the combined method would save time and expense because of the elimination of the intermediate steps.

9. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
4/19/2005

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER